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10/049,472	05/28/2002	Hiroshi Nagase	1038-02	4103

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EXAMINER	
ROYDS, LESLIE A	

ART UNIT	PAPER NUMBER
1614	

DATE MAILED: 12/30/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/049,472	NAGASE ET AL.	
	Examiner	Art Unit	
	Leslie A. Royds	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-9* is/are pending in the application.

4a) Of the above claim(s) *5-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4 and 7-9* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-9 are presented for examination.

Acknowledgment is made of Applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy was filed in the instant application on February 12, 2002. Applicant's Preliminary Amendment filed February 12, 2002 has been received and entered into the application. Accordingly, the specification at pages 18-20 and pages 22-23 and claim 4 has been amended and claims 8-9 have been added.

Applicant's "Response to Restriction and Election of Species Requirement" filed August 4, 2004 has been received and entered into the application. The election/restriction requirement dated July 9, 2004 was vacated because the instant application is a National Stage (371) application of a PCT and should have been restricted according to 371 practice. A second election/restriction requirement was sent September 23, 2004 and Applicant's "Response to Restriction and Election of Species Requirement" filed October 22, 2004 has been received and entered into the application.

Election/Restriction

Applicant's election without traverse of Group I (claims 1-4 and 7-9) and election of R^1 as a cycloalkylalkyl group with 4-7 carbon atoms, R^2 and R^3 each as a hydroxyl group, A as -XC(=Y)- where X is NR^4 and Y is O, R^4 as a straight alkyl group with 1-5 carbon atoms, B as a straight acyclic unsaturated hydrocarbon containing one double bond and 2-14 carbon atoms, R^5

as 3-furanyl, R^6 and R^7 as –O–, and R^8 as hydrogen in the reply filed on October 22, 2004 is acknowledged.

Therefore, for the reasons set forth above and of record, the restriction requirement is still deemed proper and is therefore made **FINAL**.

Upon further consideration, the election of species requirement is withdrawn and the full scope of the elected invention (Group I, claims 1-4 and 7-9) (see below) will be herein acted on the merits.

Claims 5-6 are withdrawn from further consideration pursuant to 37 C.F.R. 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim.

The claims corresponding to the elected subject matter are 1-4 and 7-9 and such claims are herein acted on the merits.

It is noted by the Examiner that claim 7 is drafted such that it includes non-elected subject matter (i.e., "obtained by an evaluation method according to claim 6") due to its dependency on claims 5 and 6. For the purposes of examination of this claim under 35 U.S.C. 112, first paragraph, claim 7 has been interpreted to incorporate all of the limitations set forth in non-elected claims 5 and 6. It is further noted by the Examiner that claim 7 is a product-by-process claim. Regarding such claims, the MPEP states, "Even though product-by-process

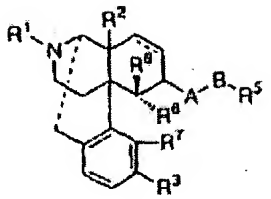
claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process" (see *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985 and MPEP §2113). Examination of claim 7 under 35 U.S.C. 102 and 103 will be performed to the extent that it is directed to a product obtained through the process of claims 5 and 6, i.e., a "product-by-process" type claim. Thus, recitation of the process by which the compound is obtained will be taken into account during examination, but it will not be considered to distinguish the compound over the prior art if said compound is found to be anticipated or obvious because the process by which it is made fails to impart any physical or otherwise material feature to said compound.

Specification

1. The disclosure is objected to because of the following informalities: reference to "Compound 1" is noted on page 27, last full paragraph, but a corresponding structural depiction or description of such a compound was not found within the specification. Appropriate correction is required.

Scope and Content of the Instant Claims

2. Claims 1-4 and 8-9 are directed towards a therapeutic agent for neuropathic pain comprising, as an active ingredient, a compound represented by the general formula (see below) or a pharmacologically acceptable acid addition salt thereof:



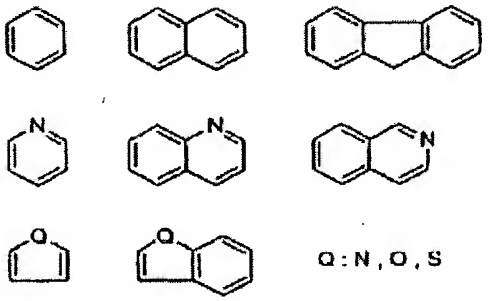
wherein the neuropathic pain is pain associated with herpes zoster. Claim 7 is directed towards a compound obtained by a method for evaluating a compound for alleviating neuropathic pain in which a neuropathic pain animal model in which pain reaction is generated by intrathecally administering the following compound: (+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octahydro –trans-quinolino[2,3-g]isoquinoline, to a mouse.

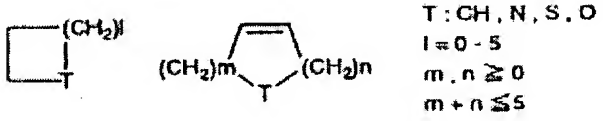
Claim 1 is representative of the therapeutic agent and recites the following limitations:

> wherein ··· represents a double bond or a single bond; R^1 represents an alkyl group having 1 to 5 carbon atoms, a cycloalkylalkyl group having 4 to 7 carbon atoms, a cycloalkenylalkyl group having 5 to 7 carbon atoms, an aryl group having 6 to 12 carbon atoms, an aralkyl group having 7 to 13 carbon atoms, an alkenyl group having 4 to 7 carbon atoms, an allyl group, a furan-2-yl-alkyl group having 1 to 5 carbon atoms, or a thiophene-2-yl-alkyl group having 1 to 5 carbon atoms; R^2 represents hydrogen, a hydroxy group, a nitro group, an alkanoyloxy group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkyl group having 1 to 5 carbon atoms, or $-NR^9R^{10}$; R^9 represents hydrogen or an alkyl group having 1 to 5 carbon atoms; R^{10} represents hydrogen, an alkyl group having 1 to 5 carbon atoms, or $-C(=O)R^{11}$; R^{11} represents hydrogen, a phenyl group, or an alkyl group having 1 to 5 carbon atoms;

R^3 represents hydrogen, a hydroxy group, an alkanoyloxy group having 1 to 5 carbon atoms, or an alkoxy group having 1 to 5 carbon atoms; A represents $-XC(=Y)-$, $-XC(=Y)Z-$, $-X-$, or $-XSO_2-$ (where each of X, Y, and Z independently represents NR^4, S, or O; R^4 represents hydrogen, a straight or branched alkyl group having 1 to 5 carbon atoms, or an aryl group having 6 to 12 carbon atoms; and each R^4 may be identical or different); B represents a valence bond, a straight or branched alkylene group having 1 to 14 carbon atoms (which may have at least one substituent selected from the group consisting of an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, a trifluoromethyl group, and a phenoxy group, where one to three methylene groups may be replaced with carbonyl groups), a straight or branched acyclic unsaturated hydrocarbon containing one to three double bonds and/or triple bonds and having 2 to 14 carbon atoms (which may have at least one substituent selected from the group consisting of an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, a trifluoromethyl group, and a phenoxy group, where one to three methylene groups may be replaced with carbonyl groups), or a straight or branched saturated or unsaturated hydrocarbon containing one to five thioether bonds, ether bonds, and/or amino bonds and having 1 to 14 carbon atoms (where any hetero atom is not directly bonded to A, and one to three methylene groups may be replaced with carbonyl groups); R^5 represents

hydrogen or an organic group having a basic skeleton selected from the group consisting of the following formulae:



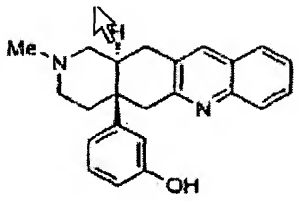


ORGANIC GROUPS REPRESENTED BY R^5

(where the organic group may have at least one substituent selected from the group consisting of an alkyl group having 1 to 5 carbon atoms, an alkoxy group having 1 to 5 carbon atoms, an alkanoyloxy group having 1 to 5 carbon atoms, a hydroxy group, fluoro, chloro, bromo, iodo, an amino group, a nitro group, a cyano group, an isothiocyanate group, a trifluoromethyl group, a trifluoromethoxy group, and a methylenedioxy group); R^6 represents hydrogen; R^7 represents hydrogen, a hydroxy group, an alkoxy group having 1 to 5 carbon atoms, or an alkanoyloxy group having 1 to 5 carbon atoms, or R^6 and R^7 together forming -O-, $-CH_2-$, or -S-; and R^8 is hydrogen; an alkyl group having 1 to 5 carbon atoms, or an alkanoyl group having 1 to 5 carbon atoms.

Claim 7 is representative of the compound and recites the following (claim 5 and 6 are also included to recite the additional limitations on which claim 7 is dependent):

> "5. A neuropathic pain animal model in which pain reaction is generated by intrathecally administering (+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octahydro-trans-quinolino[2,3-g]isoquinoline



to a mouse.

6. A method for evaluating a compound for alleviating neuropathic pain in which a neuropathic pain animal model according to Claim 5 is used.

7. A compound obtained by an evaluation method according to Claim 6."

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claim 7 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for specific compositions of defined chemical structure, i.e. therapeutic agents, comprising compounds of the general chemical structure in, eg. Claim 1, (see above in Section 1), does not reasonably provide enablement for the evaluation of an undefined compound for alleviating neuropathic pain in a neuropathic pain animal model or for a compound obtained by such evaluation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In this regard, the application disclosure and claims have been compared per the factors indicated in the decision *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) as to undue experimentation. The factors include:

1) the nature of the invention;
2) the breadth of the claims;
3) the predictability or unpredictability of the art;
4) the amount of direction or guidance presented;
5) the presence or absence of working examples;
6) the quantity of experimentation necessary;
7) the state of the prior art; and,
8) the relative skill of those skilled in the art.

The relevant factors are addressed below on the basis of comparison of the disclosure, the claims and the state of the prior art in the assessment of undue experimentation.

Factors 1 and 2) The present claims 1-4 and 8-9 are broadly directed to a therapeutic agent, or a pharmacologically acceptable acid addition salt thereof, represented by the general chemical formula set forth above in Section 1, used in the treatment of neuropathic pain, especially that which results from herpes zoster. Claim 7 is directed to a compound obtained by an evaluation method comprising intrathecal administration of (+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octahydro-trans-quinolino[2,3-g]isoquinoline to generate pain reaction in a mouse and evaluating the efficacy of said compound to alleviate neuropathic pain.

Factor 3) It is well known in the art that the algesic effects of intrathecal administration of certain drug substances, such as (+)-4a-(3-hydroxyphenyl)-2-methyl-1,2,3,4,4a,5,12,12a-octahydro-trans-quinolino[2,3-g]isoquinoline, to a mouse animal model can be monitored by applying painful stimuli and monitoring tail-flick (see Tseng et al., *Delta-1 Opioid Receptor-Mediated Antinociceptive Properties of a Nonpeptidic Delta Opioid Receptor Agonist, (-)TAN-67, in the Mouse Spinal Cord*, 1997). Similarly, it is well known in the art to monitor the efficacy of a compound in an appropriate animal model (one that is well-suited to clearly define the effects of a certain compound in a particular disease state) to determine whether it may be effective in treating one or more signs or symptoms of a particular condition. In order to establish the efficacy of a compound in treating a particular disease, it would be well within the scope of the skilled artisan to use a specific type of compound known or projected to have a certain effect on a particular condition to evaluate the efficacy of such a compound in ameliorating the condition. However, it is unlikely, due to the unpredictability of the results that may be obtained, that a person familiar with the art would evaluate the efficacy of any one or more of *all possible compounds* known to man (eg, over 10,000 known in the *Merck Index* alone (1996; cited by examiner)) in a particular disease state, most especially because it could not be guaranteed that any one or more of the plethora of existing compounds would have some or any efficacy in treating a specific condition. In order to receive any kind of predictable results, it would be necessary to identify and then test a certain subset of compounds known or suggested to have efficacy in a certain disease state rather than to test **any** compound with no known or suggested efficacy in treating a particular disease.

Furthermore, because the compounds intended for use in this evaluation method are not described, the Examiner understands from the application as originally filed that Applicant is definitively claiming all compounds that **may** have activity within the proposed neuropathic pain animal model. However, such compounds are not adequately identified and are open to all possible compounds, the majority of which are not guaranteed to have any activity within the proposed neuropathic pain animal model. As a result, the outcome of the evaluation method as proposed in the present claims is highly unpredictable given the number of the possible compounds that may be used that fall within the scope of this claim.

Factor 4) Applicant has merely disclosed that the therapeutic agent of the general chemical structure as set forth above in Section 1 can be used in the treatment of neuropathic pain, but has not set forth which, of *all possible compounds*, are intended for evaluation during the evaluation method process. The recitation of "a compound" in present claim 7 is considered by the Examiner to be language that encompasses a plethora of possible compounds, absent any further limitation within the claim restricting the scope to a certain group of therapeutic agents with a particular chemical structure and function. Based on the discussion in Section 3 above, however, the present disclosure as originally filed is clearly not adequate direction or guidance as to which compounds intended for use in this evaluation method can be employed to adequately assess the ability of a particular compound to alleviate neuropathic pain in a predictable manner.

Factor 5) The specification at pages 25-32 provides data demonstrating the production of a neuropathic pain animal model, the evaluation of the action of a proposed therapeutic agent in

inhibiting neuropathic pain, the evaluation of the action of the proposed therapeutic agent in inhibiting neuropathic pain in a sciatic nerve ligation model and the evaluation of the action of the proposed therapeutic agent in inhibiting hyperalgesia and allodynia in pain associated with zosteriform skin lesions. However, the therapeutic agent employed in the working examples of the disclosure are those of general chemical formula I (refer to Section 1 for chemical structure). The breadth of active compounds encompassed by the present claims by the recitation of "a compound" is incredibly vast and the use of one particular compound ("Compound 2", see p. 27 of Applicant's specification, last line) is not considered to be reasonably representative of the scope of *all possible* compounds encompassed by the present claims, i.e., those compounds that would be evaluated. The Examiner does not believe that the data is commensurate in scope with the claimed subject matter, since the claims encompass evaluating *all known compounds,* while Applicant's data merely shows one compound, i.e., a compound of general formula I (see Section 1 above), as being evaluated by this method for its efficacy in alleviating neuropathic pain.

Factor 6) The burden of enabling the evaluation of *all known compounds* for efficacy in alleviating neuropathic pain, especially neuropathic pain associated with herpes zoster, is much greater than that of enabling the use of a particular type of active agent that is known to have a general chemical structure and corresponding function. Since the present specification would not enable the skilled artisan to practice the evaluation method using all known compounds, especially given the breadth of all compounds encompassed by the present claims, a clear burden

of undue experimentation would be placed upon the skilled artisan in order to practice this aspect of the invention.

Factor 7) Rodent models used to monitor the effects of NMDA and substance P, chemicals which induce scratching, biting and licking behavior after intrathecal administration (see Applicant's specification, p. 3), on pain generation were well known in the art as effective animal models in which to assess the function of these chemicals. The use of a compound, known to have an particular effect on a specific condition, in an animal model in order to assess the efficacy of such a compound in ameliorating such a condition was well known in the art and allowed for predominantly predictable results if the function of the compound was well known or suggested. However, for the reasons set forth in the above sections, it is exceedingly more difficult to assess the efficacy of *any known compound* in ameliorating a condition, since it is in no way assured that any one or more of the vast majority of existing compounds may show some or any efficacy in treating a particular condition.

Factor 8) In view of the discussion of each of the preceding seven factors, the level of skill in this art is high and is at least that of a medical doctor with several years of experience in the art.

Summary

As the cited art and discussion of the above 8 factors establish, practicing the claimed method in the manner disclosed in the application would not imbue the skilled artisan with adequate knowledge as to which compounds are intended to be evaluated using the method proposed in

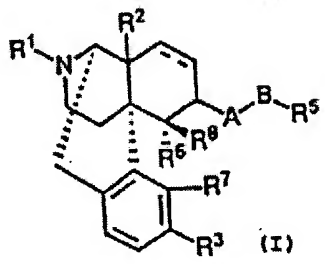
the present claims. In order to actually evaluate any of the possible compounds encompassed by the present claims, it is clear from the discussion above and the sheer number of known compounds (see *Merck Index*, 1996) that could be employed that the skilled artisan could not rely on Applicant's disclosure as required by 35 U.S.C. § 112, first paragraph. Given that the art fails to recognize and Applicant has failed to disclose those compounds that would be likely candidates for evaluation, the skilled artisan would be faced with the impermissible burden of undue experimentation in order to practice this aspect of the claimed invention. Accordingly, claim 7 is deemed properly rejected.

Claim Rejections - 35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

6. Claims 1-4 and 7-9 are rejected under 35 U.S.C. 102(b) as being anticipated by Nagase et al. in European Patent 0577847A1. Nagase et al. teaches compounds having the following general structure:



(I)

wherein:

(i) ..... represents a single or double bond;

(ii) R^1 represents an alkyl group having 1-5 carbon atoms, a cycloalkylalkyl group having 4-7 carbon atoms, a cycloalkenylalkyl group having 5-7 carbon atoms, an aryl group having 6-12 carbon atoms, an aralkyl group having 7-13 carbon atoms, an alkenyl group having 4-7 carbon atoms, an allyl group, a furan-2-ylalkyl group having 1-5 carbon atoms, or a thiophene-2-ylalkyl group having 1-5 carbon atoms;

(iii) R^2 represents a hydrogen atom, a hydroxy group, a nitro group, an alkanoyloxy group having 1-5 carbon atoms, an alkoxy group having 1-5 carbon atoms, an alkyl group having 1-5 carbon atoms, or $-NR^9R^{10}$ wherein R^9 represents a hydrogen atom or an alkyl group having 1-5 carbon atoms, and R^{10} represents a hydrogen atom; an alkyl group having 1-5 carbon atoms, or $-C(=O)R^{11}$ wherein R^{11} represents a hydrogen atom, a phenyl group or an alkyl group having 1-5 carbon atoms;

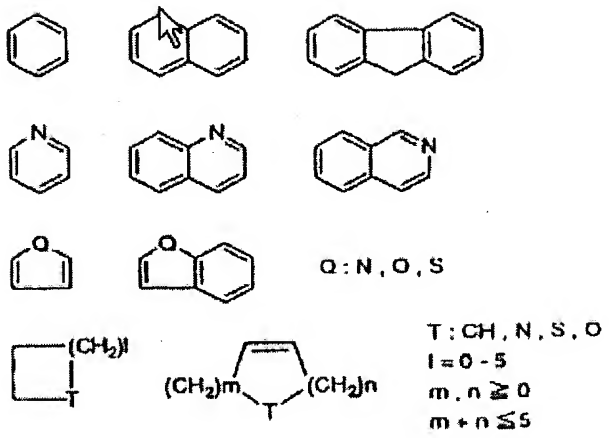
(iv) R^3 represents a hydrogen atom, a hydroxy group, an alkanoyloxy group having 1-5 carbon atoms, or an alkoxy group having 1-5 carbon atoms;

(v) A represents $-XC(=Y)-$, $-XC(=Y)Z-$, $-X-$, $-XSO_2-$, or $-OC(OR^4)R^4-$ (where, X, Y and Z each independently represent NR^4 , S or O wherein R^4 represents a hydrogen atom, a straight-chain or

branched chain alkyl group having 1-5 carbon atoms or an aryl group having 6-12 carbon atoms, and wherein R^4 may be identical or different);

(vi) B represents a valence bond, a straight-chain or branched chain alkylene group having 1-14 carbon atoms (which may be substituted with at least one type of substituent groups selected from the group consisting of an alkoxy group having 1-5 carbon atoms, an alkanoyloxy group having 1-5 carbon atoms, a hydroxy group, fluorine, chlorine, bromine, iodine, an amino group, a nitro group, a cyano group, a trifluoromethyl group and a phenoxy group, and wherein 1 to 3 methylene groups may be replaced with carbonyl groups), an acyclic unsaturated hydrocarbon containing from 1 to 3 double bonds and/or triple bonds and having 2-14 carbon atoms (which may be substituted with at least one substituent group selected from the group consisting of an alkoxy group having 1-5 carbon atoms, an alkanoyloxy group having 1-5 carbon atoms, a hydroxy group, fluorine, chlorine. bromine, iodine, an amino group, a nitro group, a cyano group, a trifluoromethyl group and a phenoxy group, and wherein from 1 to 3 methylene groups may be replaced with carbonyl groups), or a straight-chain or branched chain saturated or unsaturated hydrocarbon group containing from 1 to 5 thioether, ether and/or amino bonds and having 1-14 carbon atoms (wherein hetero atoms are not bonded directly to A, and 1 to 3 methylene groups may be replaced with carbonyl groups);

(vii) R^5 represents a hydrogen atom or an organic group having the basic skeleton of any of the following formulas:



(which may be substituted with at least one or more substituent groups selected from the group consisting of an alkyl group having 1-5 carbon atoms, an alkoxy group having 1-5 carbon atoms, an alkanoyloxy group having 1-5 carbon atoms, a hydroxy group, fluorine, chlorine, bromine, iodine, an amino group, a nitro group, a cyano group, an isothiocyanate group, a trifluoromethyl group and a methylenedioxy group),

(viii) R^6 represents a hydrogen atom; R^7 represents a hydrogen atom, a hydroxy group, an alkoxy group having 1-5 carbon atoms, an alkanoyloxy group having 1-5 carbon atoms, or R^6 and R^7 together represent -O-, -CH2- or -S-; and

(ix) R^8 represents a hydrogen atom, an alkyl group having 1-5 carbon atoms, or an alkanoyl group having 1-5 carbon atoms.

The recitation of "obtained by an evaluation method" in present claim 7 has been noted and has been identified as the process by which the product (the compound) is made. However, the process by which the compound in the instant application is made is not considered to

distinguish this compound over the composition disclosed in Nagase et al. because it fails to impart any physical or otherwise material feature to the claimed composition that is not found in the composition of the reference. See MPEP §2113 regarding product-by-process claims.

Accordingly, claims 1-4 and 7-9 are anticipated by the prior art and rejection of these claims is deemed to be proper.

Double Patenting

Obviousness-Type

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Provisional

Claims 1-4 and 7-9 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 3-8 directed to the composition claimed in copending application: 10/477,062. Provisional double patenting

rejections over the above-cited copending application are directed only to the composition claims and are not directed to any copending method claims contained within the application.

Although the conflicting claims are not identical, the claims of the instant application and those of the copending Application No. 10/477,062 are not considered to be patentably distinct from each other because the present claims clearly provide for the limitations of the copending claims. Claim 1 of the copending application recites all of the limitations of claim 1 of the present claims, with the exception of reciting Q as N**H** and not simply as N and reciting T as CH_2 and not simply CH. However, the presence of an additional hydrogen bonded to either the nitrogen atom or the carbon atom is not reasonably expected to impart an unanticipated function to the molecule that would not be reasonably expected from the compound in the present claims. In addition, claims 4-8 of the copending application recite species of the genera recited in the present claims. For example, claim 4 of the copending application recites "methyl, ethyl, propyl, butyl, isobutyl, cyclopropylmethyl, allyl, benzyl or phenethyl", which are known to be species of the following genera recited in the present claims: alkyl of 1-5 carbons, cycloalkylalkyl of 4-7 carbons, allyl, aryl of 6-12 carbons or aralkyl of 7-13 carbons (see present claim 1, lines 4-10). Claims 7 and 8 of the copending application are directed towards a morphinan quaternary ammonium salt derivative, wherein the counter ion may be an iodide ion; while this species is not specifically stated in the present claims, the present claims recite the use of any pharmacologically acceptable acid addition salt thereof, which would encompass the quaternary ammonium salt recited in the copending claims.

Furthermore, although the claims of the present application are directed towards a therapeutic agent for neuropathic pain and the claims of the copending application are directed towards a therapeutic agent for sepsis, the intended use of the compound is not considered to impart any physical or otherwise material feature to the claimed composition of the present application that is not found in the claimed composition of the copending application.

The claims of the instant application and those of the copending application are therefore not considered to be patentably distinct from each other and are rejected for obviousness-type double patenting as claiming obvious variations.

Non-Provisional

Claims 1-4 and 7-9 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the composition claims of the following 15 U.S. Patent Nos.: US-5,739,145, US-5,776,945, US-5,849,731, US-5,852,030, US-6,087,369, US-6,147,084, US-6,156,762, US-6,172,078, US-6,177,438, US-6,187,782, US-6,277,859, US-6,291,470, US-6,316,461, US-6,323,212, and US-6,440,987. This rejection is directed solely to the claims of the above-cited patents that define compositions of matter, i.e., the same statutory category of invention.

Due to the number of applicable different patents and patented claims, a detailed analysis of why the presently claimed subject matter would have been an obvious variation over each one of the applicable claims in different patents is not presented, but the rejection set forth below is

applicable to all of the above-cited patents but for differences in claim numbering. Claims 1-4 and 7-9 are rejected over claims 1 and 3-8 of U.S. Patent No. 5,244,904. For the following reasons, the presently claimed subject matter would have been obvious not only over such claims, but over each of the applicable claims of the remaining U.S. Patents cited above.

Although the conflicting claims are not identical, the claims of the instant application and those of the '904 patent are not considered to be patentably distinct from each other because the present claims clearly provide for the limitations of the patented claims. The therapeutic agents provided in the present claims clearly encompass the agents/composition(s)/compound(s) specified within the patented claims. For example:

(i) the present claims encompass compounds with the following moieties of R^1: alkyl of 1-5 carbons (methyl, ethyl, propyl, butyl, pentyl), cycloalkylalkyl of 4-7 carbons (cyclopropylmethyl, cyclobutylmethyl, cyclopentylmethyl, cyclohexylmethyl), cycloalkenylalkyl of 5-7 carbons (cyclopentenylmethyl, cyclohexenylmethyl), trans-alkenyl of 4-5 carbons (trans-2-butenyl), allyl, furanyl-2-ylalkyl of 1-5 carbons (2-furanylmethyl), and thienyl-2-ylalkyl of 1-5 carbons (2-thienylmethyl) (see patented claims 1, 3 and 8, cols.137 and 138);

(ii) the present claims encompass the following moieties of R^2 (equivalent to R^3 in the present claims): hydrogen or hydroxyl (see patented claims 1, 4 and 8, cols.137 and 138);

(iii) the present claims encompass the following moieties of R^3 (equivalent to R^5 with or without any substitution in the present claims): hydrogen atom, fluorine atom, chlorine atom, bromine atom, nitro, or alkyl of 1-5 carbons (methyl, ethyl, propyl, butyl, pentyl) (see patented claims 1, 5 and 8, cols.137 and 138);

(iv) the present claims encompass the following moieties of R^4: hydrogen atom, alkyl of 1-5 carbons (methyl, ethyl, propyl, butyl, pentyl), benzyl or phenyl (see patented claims 1, 6 and 8; cols.137 and 138); and

(v) the present claims encompass the following moieties of R^5 (equivalent to R^2 in the present claims): hydrogen, hydroxy (acetoxy), or alkanoyloxy of 1-5 carbons (propanoyloxy, butanoyloxy, pentanoyloxy) (see patented claims 1, 7 and 8, cols. 137 and 138).

Accordingly, rejection of claims 1-4 and 7-9 of the present application is deemed proper over each of the above-indicated patents as claiming obvious variations.

No claims of the present application are allowed.

Given the above rejections for double patenting, Applicant is advised to file all appropriate terminal disclaimers for each patent and application. It is also suggested that applicant provide information regarding any other patent(s) or application(s) that may impact patentability of the current application claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leslie A. Royds whose telephone number is (571)-272-6096. The examiner can normally be reached on Monday-Friday (8:30 AM-5:00 PM).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (571)-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Leslie A. Royds
Examiner
Art Unit 1614

December 22, 2004

RAYMOND HENLEY III
PRIMARY EXAMINER
AU 1614